



General

Guideline Title

Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians.

Bibliographic Source(s)

Qaseem A, Humphrey LL, Fitterman N, Starkey M, Shekelle P, Clinical Guidelines Committee of the American College of Physicians. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2013 Dec 3;159(11):770-9. [67 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the overall quality of evidence (high, moderate, low, insufficient) and strength of recommendations (strong, weak) are provided at the end of the "Major Recommendations" field.

Recommendation 1: *The American College of Physicians (ACP) recommends using a restrictive red blood cell (RBC) transfusion strategy (trigger hemoglobin threshold of 7 to 8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease (CHD).* (Grade: weak recommendation; low-quality evidence)

Low-quality evidence showed no mortality benefit of liberal compared with restrictive transfusion strategies across the patient populations studied. Most evidence did not show a substantial difference in benefit between liberal and restrictive RBC transfusions. In addition, low-quality evidence showed conflicting results for cardiovascular events. Low-quality evidence showed no mortality benefit of a higher (liberal) transfusion threshold (hemoglobin levels >10 g/dL) and fewer cardiovascular events with a lower (restrictive) transfusion threshold (hemoglobin levels of 7 to 8 g/dL) in noncardiac surgery patients. Studies showed no short-term mortality benefit in hip fracture and vascular surgery patients treated with liberal RBC transfusion compared with restrictive transfusion and found no difference in outcomes. Observational studies also failed to find a mortality benefit with aggressive liberal transfusion. For noncardiac surgeries other than hip fracture surgery, data are inconclusive. Low-quality evidence showed that patients with the acute coronary syndrome who received liberal RBC transfusions (hemoglobin threshold of 10 g/dL) had a mortality benefit compared with those who received more restrictive transfusion thresholds. However, this result was from a small study that included patients with stable and unstable CHD, and the difference was not statistically significant. Harms were sparsely reported, and no trials reported a difference in adverse events for liberal compared with restrictive transfusions.

Recommendation 2: ACP recommends against the use of erythropoiesis-stimulating agents (ESAs) in patients with mild to moderate anemia and congestive heart failure (CHF) or CHD. (Grade: strong recommendation; moderate-quality evidence)

The harms outweigh the benefits for treating patients with mild to moderate anemia using ESAs. The potential harms associated with ESA therapy include increased risk for thromboembolic events shown in 3 studies and a suggestion of increased stroke rates in 1 study. Although anemia is common in patients with CHF and CHD, high-quality evidence showed that treatment with ESAs did not improve mortality or affect cardiovascular events or hospitalizations, and moderate-quality evidence showed no improvement for quality of life. Baseline hemoglobin levels for study patients ranged from 9 to 10 g/dL.

Definitions:

Grading of Quality of Evidence

High-Quality Evidence: Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized, controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect.

Moderate-Quality Evidence: Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on confidence in the estimate of effect and may change the estimate.

Low-Quality Evidence: Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose-response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

Insufficient Evidence to Determine Net Benefits or Risks: When the evidence is insufficient to determine for or against routinely providing a service, the recommendation is graded as "insufficient evidence to determine net benefits or risks." Evidence may be conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect that is very uncertain as evidence is either unavailable or does not permit a conclusion.

The American College of Physicians Guideline Grading System*		
Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced with Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

*Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Anemia and iron deficiency associated with heart disease (coronary heart disease [CHD] and congestive heart failure [CHF])

Guideline Category

Management

Treatment

Clinical Specialty

Cardiology

Family Practice

Geriatrics

Hematology

Internal Medicine

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To present the evidence and provide clinical recommendations on the treatment of anemia and iron deficiency in adult patients with heart disease

Target Population

Anemic or iron deficient adult patients with heart disease

Interventions and Practices Considered

1. Red blood cell (RBC) transfusion (liberal versus restrictive transfusion strategies)
2. Erythropoiesis-stimulating agents (ESAs) (not recommended for mild-to-moderate anemia)
3. Intravenous iron (considered but no recommendation made because of insufficient evidence)

Major Outcomes Considered

- Mortality (all-cause and disease-specific)
- Hospitalization (all-cause and disease-specific)
- Exercise tolerance
- Quality of life

- Cardiovascular events (defined as myocardial infarction, congestive heart failure exacerbation, arrhythmia, cardiac death)
- Harms, including hypertension, venous thromboembolic events, ischemic cerebrovascular events

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): A systematic evidence review was prepared by the Evidence-based Synthesis Program Center (EPC) at the Portland Veterans Affairs Medical Center, Portland, OR for the Department of Veterans Affairs, Veterans Health Administration, Health Services Research & Development Service (see the "Availability of Companion Documents" field).

Data Sources and Searches

The EPC staff conducted a search for literature published in MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from database inception to August 2012. They searched EMBASE through November 2010 because they could not retain a license for this database beyond that time frame. The search strategy included such terms as *anemia*, *congestive heart failure*, *coronary heart disease*, *ischemic heart disease*, *erythropoiesis-stimulating agents (ESAs)*, *iron*, and *red blood cell transfusion*. The detailed search strategy is provided in Table 1 of the Supplement (see the "Availability of Companion Documents" field). Additional articles were obtained from systematic reviews; reference lists of pertinent studies, reviews, and editorials; and consulting experts. The review team also searched for ongoing and recently completed studies on ClinicalTrials.gov and included reports of trials that had been published as of April 2013.

Study Selection

The analytic framework that guided the review and synthesis of the literature is provided in Appendix Figure 1 of the systematic evidence review. Eligible articles had English-language abstracts and provided primary data about the effects of ESAs, iron, or blood transfusions in adult populations with anemia (hemoglobin levels <13 g/dL in men and <12 g/dL in women) and symptomatic congestive heart failure (CHF) (with or without decreased systolic function) or coronary heart disease (CHD) (the acute coronary syndrome, the post-acute coronary syndrome, and history of myocardial infarction [MI] or angina). Trials with mixed populations of patients with and without anemia were included as long as data specific to the anemia subgroup were reported. Trials comparing interventions with placebo or those comparing more intensive with less intensive interventions (that is, trials examining different transfusion thresholds or hemoglobin targets) were also included. Because few trials of red blood cell transfusion were found, the review team included observational studies to characterize the evidence on which current transfusion practice is based. Outcomes of interest included mortality, hospitalization, exercise tolerance, cardiovascular events, quality of life, and adverse effects of treatment.

Three investigators reviewed the titles and abstracts of citations identified from literature searches, and 2 reviewers independently assessed the selected full-text articles for inclusion on the basis of the eligibility criteria shown in Table 2 of the Supplement. Disagreements were resolved by consensus.

Number of Source Documents

Fifty-five articles comprising 52 primary studies met inclusion criteria.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Quality of Evidence

High-Quality Evidence: Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized, controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect.

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Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): A systematic evidence review was prepared by the Evidence-based Synthesis Program Center at the Portland Veterans Affairs Medical Center, Portland, OR for the Department of Veterans Affairs, Veterans Health Administration, Health Services Research & Development Service (see the "Availability of Companion Documents" field).

Data Extraction and Quality Assessment

From each study, the evidence review team abstracted study design, objectives, setting, population characteristics (including sex, age, left ventricular ejection fraction, baseline New York Heart Association [NYHA] class, and coronary heart disease [CHD] definition), participant eligibility and exclusion criteria, number of participants, years of enrollment, duration of follow-up, the study and comparator interventions, important co-interventions, baseline hemoglobin levels, change in hemoglobin levels, health outcomes, and adverse effects. If only the hematocrit was reported, the reviewers used a conversion of 3:1 to approximate the hemoglobin value. To evaluate harms, data on adverse effects were collected from all included trials and specifically gathered data from each erythropoiesis-stimulating agent (ESA) trial on hypertension, venous thromboembolic events (including deep venous thrombosis, pulmonary embolism, and vascular access thrombosis), and ischemic cerebrovascular events. In trials examining blood transfusions, reviewers specifically looked for reporting of transfusion reactions.

Two reviewers independently assessed the quality of each trial using a tool developed by the Cochrane Collaboration. Disagreements were resolved by discussion. Each study was given an overall summary assessment of low, high, or unclear risk of bias. Reviewers assessed the overall quality of evidence for outcomes using a method developed by the Grading of Recommendations Assessment, Development and Evaluation Working Group (see the "Rating Scheme for the Strength of the Evidence" field), which considers the consistency, coherence, and applicability of a body of evidence, as well as the internal validity of individual studies, to classify the grade of evidence across outcomes.

Although there is no widely accepted standard for quality assessment of observational studies, the reviewers adapted existing tools relevant to this review and specifically assessed whether each observational blood transfusion study conducted an analysis adjusting for patient propensity to receive a blood transfusion, accounted for bleeding complications (regardless of whether they were procedure-related), and accounted for the timing of transfusion given the potential for survival bias in which patients who died could not have received a transfusion. The detailed assessment of quality for each study is provided in Tables 3 to 6 of the Supplement (see the "Availability of Companion Documents" field). An overall summary assessment for observational studies was not reported because there are no validated criteria for doing so.

Data Synthesis and Analysis

The review team did meta-analyses of study-level data evaluating the effects of liberal compared with restrictive transfusion strategies on short-term mortality rates (defined as death during or within 30 days after the hospital stay) and cardiovascular events (defined as myocardial infarction [MI], congestive heart failure [CHF] exacerbation, arrhythmia, or cardiac death—in-hospital events were distinguished from those occurring during longer-term follow-up). The number of events and total participants were abstracted from each treatment group and a pooled estimate of relative risk (RR) was obtained using a random-effects model. The reviewers preferentially used 30-day mortality for the analysis, followed by in-hospital and 72-hour mortality. A sensitivity analysis was conducted on the basis of the definition of short-term mortality. If trials included mixed populations of patients with and without heart disease, authors were contacted for subgroup information if it was not available in published reports.

The review team also did meta-analyses of ESA trials for each of the following outcomes: mean difference in the change in NYHA class, exercise duration during the 6-minute walk test, all-cause mortality, hospitalizations, cardiovascular events, hypertension events, and ischemic cerebrovascular events. Given the variety of assessment tools used, the team did not do meta-analyses of quality-of-life outcomes. Sensitivity analyses were run for all outcomes, excluding studies with high or unclear risk of bias.

All analyses were done using Stata 10.0 (StataCorp, College Station, Texas). Statistical heterogeneity among the trials combined in meta-analysis was assessed by the Cochran *Q* test and *I*² statistic. Publication bias was not assessed because of the small number of trials that could be combined. The review team qualitatively synthesized the results of trials of iron therapy because only 3 trials examined the effects of iron, with 1 large trial dominating.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This guideline is based on a systematic evidence review and summary paper that addressed the following key questions related to the treatment of anemia in patients with heart disease:

- 1. In patients with congestive heart failure (CHF) or coronary heart disease (CHD), what are the health benefits and harms of treating anemia with red blood cells (RBC) transfusions?
- 2. In patients with CHF or CHD, what are the health benefits and harms of treating anemia with erythropoiesis-stimulating agents (ESAs)?
- 3. In patients with CHF or CHD, what are the health benefits and harms of using iron to treat iron deficiency with or without anemia?

Rating Scheme for the Strength of the Recommendations

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Quality of Evidence	Strength of Recommendation	
* Adapted from the Evidence Group.	classification developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group.	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced with Risks and Burden

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was approved by the American College of Physicians (ACP) Board of Regents on 30 July 2013.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

See the "Benefits" sections in the original guideline document for specific benefits of treating anemia with red blood cell (RBC) transfusion and erythropoiesis-stimulating agents (ESAs) and treating iron deficiency with intravenous iron.

Potential Harms

See the "Harms" sections in the original guideline document for specific harms of treating anemia with red blood cell (RBC) transfusion and erythropoiesis-stimulating agents (ESAs) and treating iron deficiency with intravenous iron.

Qualifying Statements

Qualifying Statements

- Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All American College of Physicians (ACP) clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.
- The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the U.S Department of Veterans Affairs.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

Patient Resources

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Qaseem A, Humphrey LL, Fitterman N, Starkey M, Shekelle P, Clinical Guidelines Committee of the American College of Physicians. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2013 Dec 3;159(11):770-9. [67 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Dec 3

Guideline Developer(s)

American College of Physicians - Medical Specialty Society

Source(s) of Funding

Financial support for the development of this guideline comes exclusively from the American College of Physicians (ACP) operating budget.

Guideline Committee

Clinical Guidelines Committee of the American College of Physicians

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Potential Conflicts of Interest: Dr. Shekelle: *Grants:* Agency for Healthcare Research and Quality, Veterans Affairs, Centers for Medicare & Medicaid Services, Office of the National Coordinator for Health Information Technology; *Personal fees:* ECRI Institute, Veterans Affairs, UpToDate. All other authors have no disclosures.

Disclosures can also be viewed at www.acponline.org/authors/icnje/ConflictOfInterestForms.do?msNum=M13-1830 .

A record of conflicts of interest is kept for each Clinical Guidelines Committee meeting and conference call and can be viewed at www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm .

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the [Annals of Internal Medicine Web site](#) .

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

Availability of Companion Documents

The following are available:

- Qaseem A, Snow V, Owens DK, Shekelle P. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. *Ann Intern Med.* 2010 Aug 3;153(3):194-199. Electronic copies: Available from the [Annals of Internal Medicine Web site](#) .
- Kansagara D, Dyer E, Englander H, Fu R, Freeman M, Kagen D. Treatment of anemia in patients with heart disease. A systematic review. *Ann Intern Med.* 2013;159:746-57. Electronic copies: Available from the [Annals of Internal Medicine Web site](#) .

- Kansagara D, Dyer E, Englander H, Freeman M, Kagen D. Treatment of anemia in patients with heart disease: a systematic review. VA-ESP Project no. 05-225. Washington (DC): Department of Veterans Affairs; 2011 Oct. 82 p. Electronic copies: Available from the [Health Services Research & Development Service Web site](#) .
- Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. Continuing Medical Education. Available from the [Annals of Internal Medicine Web site](#) .

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

A collection of Recommendation Summaries for all current American College of Physicians Clinical Guidelines is now available for download to mobile devices from the [American College of Physicians Web site](#) .

Patient Resources

The following is available:

- Summaries for patients. Treatment of anemia in patients with heart disease: a clinical practice guideline From the American College of Physicians. Ann Intern Med 2013 Dec 3;159(11):I-32. Electronic copies: Available from the [Annals of Internal Medicine Web site](#) .

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

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NGC Status

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